

Retrospective Review of Serum Creatinine and Creatinine-Based Measures of Estimated Glomerular Filtration Rate in an Amputee Population

Capt Ellen E. Im, USAF MC*; Capt Ian J. Stewart, USAF MC*; Capt Benjamin D. Morrow, USAF MC*; Maj Molly A. Tilley, USAF MC*; Capt Kelly D. Heegard, USAF MC*; James K. Aden, PhD†; LTC Kevin K. Chung, MC USA†; Casey L. Cotant, MD*

ABSTRACT A variety of equations are used to estimate glomerular filtration rate (eGFR). These formulas have never been validated in the setting of traumatic amputation. In this retrospective study involving 255 military personnel with traumatic amputations at a single outpatient center, muscle mass lost was estimated using percentage of estimated body weight lost (% EBWL). Serum creatinine (Scr) and eGFR by the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations were compared to % EBWL for each patient. The average Scr for the group studied was also compared with a cohort matched for age, sex, and race from the Third National Health and Nutrition Examination Survey (NHANES III). Percentage EBWL correlated significantly with Scr ($R^2 = 0.095$, $p < 0.0001$), eGFR by MDRD ($R^2 = 0.077$, $p < 0.0001$), and eGFR by CKD-EPI ($R^2 = 0.074$, $p < 0.0001$). The average Scr was significantly lower than a similar population from NHANES III (0.83 ± 0.137 mg/dL vs. 1.14 ± 0.127 mg/dL, $p < 0.0001$). Percentage EBWL has a significant correlation with Scr and eGFR by both the MDRD and CKD-EPI equations. Furthermore, patients with traumatic amputation have significantly lower Scr values than the general population. Creatinine-based estimators of GFR may overestimate renal function in the setting of traumatic amputation.

INTRODUCTION

Approximately 1.6 million Americans live with an amputation, 45% of which are related to trauma.¹ This has gained special attention in the military, as an estimated 1,621 U.S. military personnel have lost limbs as a result of combat operations in Iraq and Afghanistan.² Victims of traumatic amputations are potentially at risk for developing kidney injury from volume depletion, exposure to nephrotoxic medications, and infection. Because estimated glomerular filtration rate (eGFR) is an important factor in guiding safe and adequate therapy, it is important to have the capability to accurately assess renal function in this population. Additionally, estimation of GFR will be essential for accurate disease surveillance as these patients age and develop other risk factors for chronic kidney disease (CKD), such as hypertension and diabetes.^{3,4}

Creatinine production is determined by lean muscle mass and is a key component in the most commonly used formulas to calculate eGFR. These formulas include the Cockcroft-Gault, the 4-variable Modification of Diet in Renal Disease (MDRD), and the CKD Epidemiology Collaboration (CKD-EPI) equations.⁵⁻⁷ Each equation uses demographic factors (age, race, and sex), serum creatinine (Scr), and, in the case of the Cockcroft-Gault equation, weight.⁵⁻⁷ The eGFR based on MDRD is commonly reported with routine laboratory tests

such as the basic metabolic panel,^{8,9} but it has been shown to underestimate measured GFR (mGFR) at values from 60 to 119 mL/min/1.73 m².¹⁰ The CKD-EPI equation has been validated as a more accurate measure of eGFR in patients with GFR > 60 mL/min/1.73 m² and also provides less bias across different subgroups.¹¹ Although these formulas have been validated and are widely used, they have not been studied in amputees who, as a result of their injury, have a reduction in muscle mass.

We sought to determine whether there was a relationship between Scr or eGFR (by MDRD and CKD-EPI equations) and percentage of estimated body weight lost (% EBWL) in U.S. military personnel who suffered traumatic amputations. We also compared the average Scr value in our patients to that of a historic control group, hypothesizing that limb loss would lower Scr values independent of renal function. Since these patients would not be expected to have better renal function than the average population, a lower average Scr would suggest that Scr-based measures overestimate GFR in patients with traumatic amputation.

METHODS

A retrospective cross-sectional study of U.S. military amputees was conducted at the Center for the Intrepid at Fort Sam Houston, Texas. The Center for the Intrepid provides comprehensive physical rehabilitation for U.S. military veterans who have suffered traumatic amputations and other debilitating injuries. After obtaining approval from our local institutional review board, we examined the records of 392 patients enrolled at this facility from July 1, 2006 to January 31, 2010.

*San Antonio Military Medical Center, 2200 Bergquist Drive, Suite 1, 59MDOS/SGO5K, Lackland AFB, TX 78236-9908.

†United States Army Institute of Surgical Research, 3698 Chambers Pass, Fort Sam Houston, TX 78234-6315.

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All Scr values obtained since the date of amputation were analyzed and averaged. Scr values associated with acute kidney injury defined by Acute Kidney Injury Network criteria¹² or renal replacement therapy were excluded. If only one Scr value was available, it served as the average for that patient. Patients without a recorded Scr were not included for analysis. Demographic variables (age, sex, and race) and level of amputation were also collected. To determine % EBWL for each patient given their respective amputations, we used the method described by Osterkamp¹³ that uses anthropometric measurements and body weight proportions of different limb segments based on cadaver data (Table I). If subjects lost multiple limbs, these percentages were summed.

To examine the relationship between % EBWL and Scr, eGFR by the 4 variable MDRD, and eGFR by CKD-EPI, linear regression was performed and an R^2 statistic was computed for each of the three dependent variables. To compare the Scr values of our patient population to that of the general population, we averaged the Scr values and compared them to a similarly aged group of patients, matched for sex and race, from the Third National Health and Nutrition Examination Survey (NHANES III) using a standard t -test.¹⁴

RESULTS

A total of 255 patients were included for analysis. Baseline characteristics are summarized in Table II. The data are reported as three scatter plots showing the relationships between % EBWL and Scr, eGFR by MDRD, and eGFR by CKD-EPI (Figs. 1–3). The R^2 values from linear regression of Scr, MDRD, and CKD-EPI in relationship to % EBWL were 0.095 ($p < 0.0001$), 0.077 ($p < 0.0001$), and 0.074 ($p < 0.0001$), respectively. In the second portion of the analysis, the average Scr of our patient population was compared with that from a matched group of nonamputees in the NHANES III database. The majority of the patients were white males (95.7%) who, as a group, had an average Scr of 0.83 ± 0.137 mg/dL. A similarly aged group of white males (874 patients) from the NHANES III data had an average Scr of 1.14 ± 0.127 mg/dL. This difference was highly statistically significant with a $p < 0.0001$. To achieve a cohort with similar age characteristics from the NHANES data, we used an upper limit for age

TABLE II. Patient Characteristics

Characteristic	
Age (Years)	29.51 \pm 7.27
Male (%)	95.7
African American (%)	9.4
Scr (mg/dL)	0.83 \pm 0.15
% EBWL	7.84 \pm 6.56

Values are expressed as mean \pm standard deviation or percentage.

of 40 years old. Since the study had 17 patients older than 40, the groups were not completely comparable. However, repeat analysis that did not include these patients did not significantly change the results (data not shown).

DISCUSSION

The results demonstrate a correlation between % EBWL and Scr, as well as Scr-based measures of eGFR, in patients with traumatic amputation. Furthermore, Scr values are significantly lower in the study population than that seen for the general population, matched for age, sex, and race. In follow-up studies to validate the CKD-EPI equation, Stevens et al assessed the variables of diabetes, transplant, and weight in different subgroups and compared both MDRD and CKD-EPI to mGFR. They found that the CKD-EPI equation overestimated mGFR in the subgroup of patients with a body mass index < 20 .^{11,15} The authors proposed that other factors must be accounting for the overestimation, such as malnutrition or decreased muscle mass. Poggio et al¹⁶ studied the use of the Cockcroft-Gault and the MDRD formulas for eGFR in critically ill patients compared to mGFR using iothalamate. They demonstrated overestimation of GFR using Scr with these formulas, which might be attributable to malnutrition and muscle wasting in the critically ill population. Taken together, these results suggest systematic overestimation of eGFR in certain populations with the MDRD and CKD-EPI equations. Although our patients have initially lost limbs and not just lean muscle, our study implies that the same problem of renal function overestimation occurs in patients with amputations.

The present study demonstrates that there is a statistically significant correlation between % EBWL and Scr. Consequently the eGFR by commonly clinically used estimating equations (MDRD and CKD-EPI) is positively correlated with % EBWL. If the eGFR was valid, one would not expect a statistically significant correlation with % EBWL. The R^2 values from the regression analyses, which represent the fraction of the variation in Scr or eGFR accounted for by % EBWL, are low, implying that other factors not considered in the study are influencing the relationship. It should be emphasized, however, that a low R^2 value does not imply the absence of a relationship but rather incompleteness of the regression model. It is possible that our method was not sufficiently accurate in defining the amount of muscle mass

TABLE I. Percentage of EBWL by Level of Amputation

Level of Amputation	% EBWL
Partial Hand	0.35
Hand/Wrist Disarticulation	0.7
Partial Foot	0.75
Foot	1.5
Below Elbow	1.5
Above Elbow	3.65
Below-Knee Amputation	3.7
Knee Disarticulation	4.4
Above-Knee Amputation	10.95
Hip Disarticulation	16

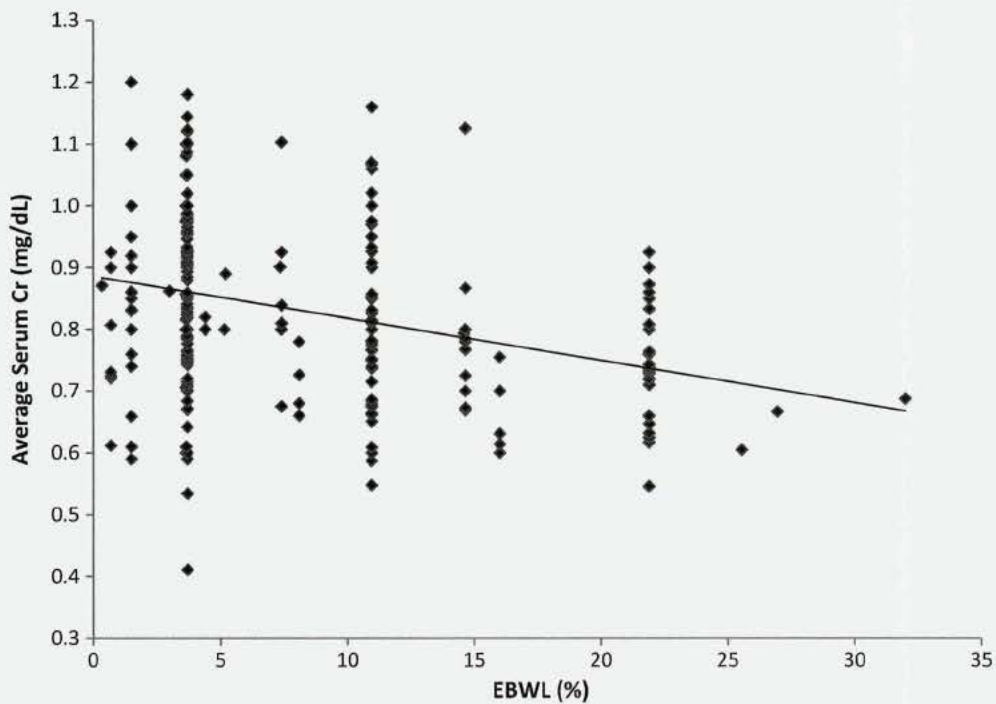


FIGURE 1. Scatter plot for average Scr and % EBWL. $R^2 = 0.095$, $p < 0.0001$.

lost or that the amount of muscle mass lost as a result of amputation cannot fully account for changes in Scr (and subsequent Scr-based estimating equations). Our attempts to estimate loss of muscle mass were further complicated by the fact that the Osterkamp method does not adjust for

race and gender. As discussed above, our findings show that Scr values in the setting of traumatic amputation are lower than one would expect on the basis of historical controls. Although we do not know the patient's true renal function, it seems unlikely that the lower Scr actually

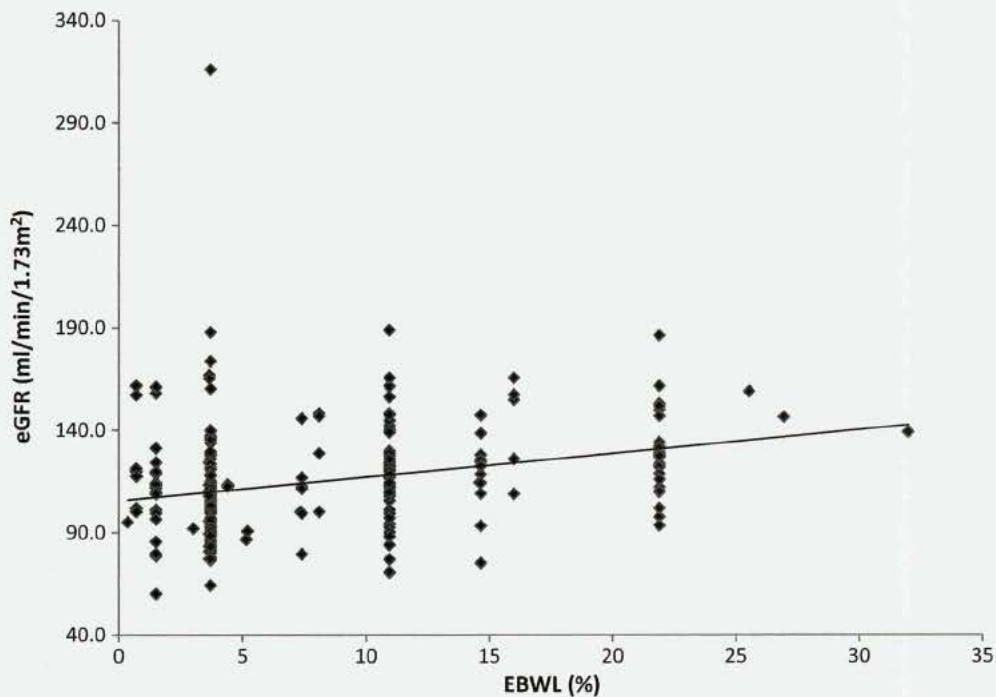


FIGURE 2. Scatter plot for eGFR by the 4 variable MDRD equation and % EBWL. $R^2 = 0.077$, $p < 0.0001$.

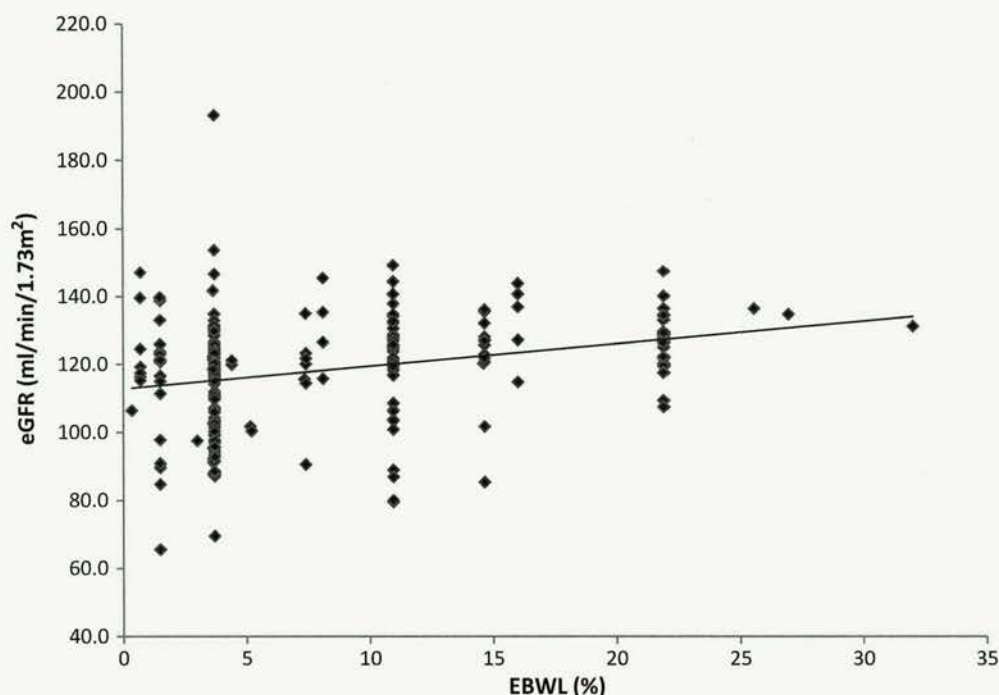


FIGURE 3. Scatter plot for eGFR by the CKD-EPI equation and % EBWL. $R^2 = 0.074$, $p < 0.0001$.

represents an improvement in GFR. It is possible that this patient population has decreased Scr production not just as a result of muscle mass lost from amputation, but the Scr may be further reduced by low protein intake, malnutrition, muscle atrophy, and immobility after amputation. An alternate hypothesis for the lower Scr values seen in our patient population compared to historical controls is that amputation results in hyperfiltration, but this hypothesis seems to lack biological plausibility.

Our results imply that Scr is a poor biomarker of steady-state renal function in the traumatic amputee population, which has implications for both drug dosing and CKD surveillance. Many of these patients are on antibiotics for infections (in either the immediate postinjury period or during the subsequent hospital and rehabilitation course), and potential overestimation of renal function by Scr-based measures could lead to errors in antibiotic dosing. Furthermore, as these patients age, they will be subject to population-wide risk factors for CKD, in addition to any risk of CKD possibly conferred by episodes of acute kidney injury occurring in the setting of the original injury and subsequent recovery period.¹⁷ In this setting, Scr-based measures to estimate GFR could result in an underestimation of the extent and severity of CKD in this potentially vulnerable group. Future research should focus on finding an alternate biomarker, such as cystatin C, to more accurately estimate renal clearance in the traumatic amputee population.^{18,19} Alternatively, efforts could focus on correlating mGFR with other variables to establish a correction factor for existing formulas.

Our study has a variety of limitations. First, it is a retrospective review and, as such, is subject to all limitations inherent in that form of study. Second, we did not measure GFR. This would have differentiated low Scr values because of decreased Scr production from increased GFR from hyperfiltration. Furthermore, there are likely to be limitations to using % EBWL as a surrogate to change in muscle mass. Anthropometric variables, including weight, are poor estimators of muscle mass.²⁰ Since our surrogate for muscle mass lost was % EBWL, it is subject to this limitation. Additionally, the use of NHANES III data as a comparator to our group might not have been completely accurate. We did not have sufficient data to match the patients on the variables of body mass index, serum albumin, or nutritional status. Nor did we have potentially useful information such as the patient's medication records, though most medications that affect creatinine cause a rise in the value. Finally, caution must be used when applying these results to other populations. Individuals with amputations as a result of vascular disease or cancer often have poor functional status and low muscle mass at baseline; therefore, the loss of a limb may not result in a dramatic change in Scr.

In summary, our retrospective analysis of patients with traumatic limb amputations demonstrates that % EBWL has a statistically significant, though incomplete, relationship with Scr and Scr-based measures of eGFR. Furthermore, the average Scr values in the post-traumatic amputee population are lower than those of the population as a whole. Future studies should probe the utility of alternate biomarkers, such as cystatin C, for estimating renal function in patients with traumatic amputations.

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